January 8, 1999

This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

NPC

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January 26, 1998

Ms. Mary Begley
Chemical Review Manager- ODM
Special Review and Reregistration Division (H7508W)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Dear Ms. Begley:

On behalf of Gowan Company, I am submitting preliminary cholinesterase results obtained from a recently completed 7-day dermal toxicity study in rats with oxydemeton-methyl (ODM, also known as Metasystox-R™). A final report will be submitted shortly. The USEPA issued a Hazard Identification Report for ODM on July 24, 1997. In that document, the HAZID committee applied an extra Uncertainty Factor of 10 based on the reviewers concerns related to mutagenic and delayed neurotoxic potential, steep dose response, use of male volunteers only in the human exposure study, and some animal brain cholinesterase inhibition at dose levels below those causing inhibition of plasma or red blood cell ChE. Gowan Company previously submitted scientific justification to the Agency regarding the inappropriate use of these components as the basis for adding an additional 10x Uncertainty Factor (UF). The current submission fully corroborates our previous arguments regarding the inappropriate use of the above factors.

In the submitted document, Gowan Company indicated that a new 7-day dermal toxicity study in rats with ODM would be conducted. The major purpose of this study was to further resolve the issues regarding brain cholinesterase as the most sensitive indication of ODM exposure and the supposition that females are more sensitive to the cholinesterase inhibiting effects of ODM than males. The 7-day dermal study has recently completed. This document submits preliminary data for plasma, whole blood, true RBC and brain cholinesterases.

Briefly, groups of 10 male and 10 female rats were exposed to dermal doses of 0, 1.5, 5, 10 or 20 mg/kg/day for seven consecutive days. Prior to study initiation and at the end of the dosing period, blood samples were evaluated for whole blood, plasma and true RBC cholinesterase. At the terminal interval, the rats were sacrificed and the brain tissue from each rat was assayed for cholinesterase activity. The cholinesterase activities were determined using a photometric assay based on a modification of the Ellman reaction on a Hitachi 911 Chemistry analyzer. Draft mean cholinesterase data tables are attached.

Plasma cholinesterase was not affected by ODM at doses of up to 20 mg/kg/day for seven consecutive days in male or female rats. Small but statistically significantly lower than control RBC (-11.6%), whole blood (-10%) and brain (8.2%) cholinesterase were seen in male rats receiving 10 mg/kg/day. Similarly, minimally lower than control RBC (-10%, not statistically significant), whole blood (-13.3%, statistically significant) and brain (-13.8%, statistically significant) cholinesterase values were seen in females treated with 20 mg/kg/day. In male rats receiving 20 mg/kg/day, statistically significantly lower than control RBC (-25%), whole blood (-19.6%) and brain (-12.3%) were seen. The No Observable Effect Level (NOEL) for cholinesterase inhibition for males rats is at least 5.0 mg/kg/day while the NOEL for females is at least 10 mg/kg/day.

This study is important for two reasons. First, the results of this study demonstrate that **male** rats are more sensitive to ODM effects on cholinesterases than **females**. Further, brain cholinesterase was not inhibited at doses lower than doses which inhibit RBC, whole blood and plasma cholinesterase. Therefore, this study provides further support to Gowan's previous arguments that "females may be more sensitive than males" and that "brain cholinesterase is the most sensitive indicator of cholinesterase inhibition" are **not** valid criteria for adding the additional 10x UF for ODM.

Secondly, in the Hazard Identification Report, the EPA review committee recommended using 14-day rat dermal study performed in 1987 as the critical study for the short-term occupational or residential exposure risk assessment of ODM. Gowan Company noted several technical concerns related to the conduct of that 14-day study. This 7-day dermal study is responsive to these concerns. The 7-days duration was selected as this is the maximum duration for the Short-Term Occupational or Residential Exposure Assessment.

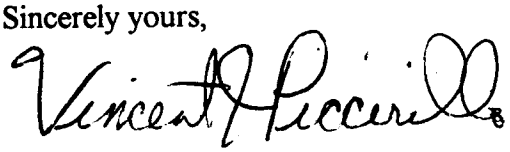
Because of the inadequacies of the old 14-day dermal study, the Gowan Company stated previously that this study was inappropriate for risk characterization purposes. Upon review of the current ODM database at that time, Gowan Company determined that the human exposure study was the most appropriate existing study for the short-term occupational or residential exposure assessment. Gowan discussed conducting the 7-day dermal study with EPA in a conference call on October 29, 1997 and EPA agreed that a new study was appropriate. Gowan submitted the protocol to EPA for review prior to study initiation and was assured that the protocol was suitable.

Results from the current 7-day dermal study demonstrate unequivocally that the 14-day study was flawed. As noted above, the NOEL for cholinesterase inhibition was 5.0 mg/kg/day for male rats. Appropriately, a 10x UF should be applies for intraspecies variation and an additional 10x UF should be applied for interspecies variation. Therefore, the short term RfD [(5.0 mg/kg)/100] should be 0.05 mg/kg/day.

On the basis of this submission, it is imperative that Gowan Company receive a written report of the second HAZID meeting (Hazard Identification Report) as soon as possible. This report should be sent to Elizabeth Codrea at Gowan Company.

Should you have any questions regarding this document, please feel free to contact Ms. Codrea (520-819-1543).

Sincerely yours,



Vincent J. Piccirillo, Ph.D., DABT
Consulting Toxicologist

cc. Elizabeth Codrea, Gowan Company

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